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Health and Environmental
Effects Profile for Ametryn

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR AMETRYN

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16. ABSTRACT The Health and Environmental Effects Profile for <u>ametryn</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. <u>Ametryn</u> has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for <u>ametryn</u> is 1×10^{-2} (mg/kg bw/day) for oral exposure.		
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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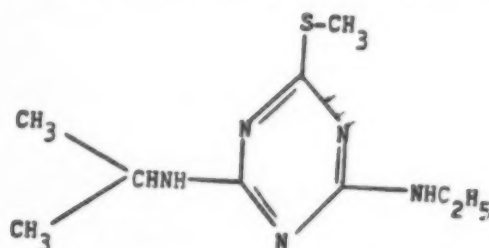
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
K _{oc}	Soil sorption coefficient
LC ₅₀	Concentration lethal to 50% of recipients (and all other subscripted dosage levels)
LD ₅₀	Dose lethal to 50% of recipients (and all other subscripted dosage levels)
ppm	Parts per million
TLC	Thin layer chromatography
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Ametryn (ametryne) is the common name for 2-ethylamino-4-isopropylamino-6-methylthio-1,3,5-triazine. Other chemical synonyms include N-ethyl-N'-(1-methylethyl)-6-(methylthio)-1,3,5-triazine-2,4-diamine, 2-(ethylamino)-4-(iso-propylamino)-6-(methylthio)-s-triazine and 2-ethylamino-4-isopropylamino-6-methylmercapto-s-triazine. This herbicide was introduced in 1964 by J. R. Geigy, Ltd. under the code number 634162, and trade names Evik (United States) and Gesapax (Canada and Europe) (BCPC, 1977; WSSA, 1979). The structural and molecular formulae for ametryn are as follows:



Molecular formula: $C_9H_{19}N_5S$

Molecular weight: 227.3

The Chemical Abstract Services (CAS) Registry number for ametryn is 834-12-8.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Ametryn is a white to colorless, crystalline compound. Selected physical properties are listed below:

Melting point:	84-85°C	(WSSA, 1979)
Vapor pressure:		(WSSA, 1979)
Temperature, °C	mm Hg	
10	1.9×10^{-7}	
20	8.4×10^{-7}	
30	3.3×10^{-6}	
50	3.9×10^{-5}	

Soil adsorption coefficient, K_{oc}		
experimental	329	(Kenaga, 1980)
calculated	250	(Kenaga, 1980)
Bioconcentration factor prediction:		(Kenaga, 1980)
from water solubility	33	
from K_{oc}	21	
Water solubility at 20°C	185 mg/l	(BCPC, 1977)
	185 ppm	(WSSA, 1979)

Ametryn is readily soluble in organic solvents. It is stable in slightly acidic or alkaline media, but is slightly hydrolyzed to the herbicidally inactive 6-hydroxy derivative in strong acidic or strong alkaline media (BCPC, 1977). It is subject to decomposition by UV irradiation, but under normal field conditions photodecomposition would be minimal (WSSA, 1979).

1.3. PRODUCTION DATA

Ametryn is synthesized by reacting atrazine with methanethiol in the presence of an equivalent of NaOH or by reacting 2-ethylamino-4-isopropylamino-6-mercapto-1,3,5-triazine with a methylating agent in the presence of NaOH (BCPC, 1977).

The sole domestic producer of ametryn is Ciba-Geigy Corp., McIntosh, AL (SRI, 1983; USITC, 1983). Current production figures are not available. In 1975, domestic consumption was estimated to be 2.0 million pounds (SRI, 1976). It has been reported that 0.37 million pounds of ametryn are annually used in Hawaii for pineapple and sugarcane crops (Goswami and Green, 1975).

1.4. USE DATA

Ametryn is used as a pre- and post-emergence selective herbicide for the control of broadleaf and grass weeds in pineapple, sugarcane and bananas (BCPC, 1977; WSSA, 1979). It can also be used as a post-directed spray in

corn, as a potato vine desiccant and as a herbicide for citrus, stone and pome fruits and coffee. Rates of application vary with use, but are commonly in the range of 1-8 lb/A. The usual carrier for spray application is water (20-40 gal/A).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

The photochemistry and photodegradation of ametryn in aqueous solutions has been studied by several investigators (Rejto et al., 1983; Burkhard and Guth, 1976; Ruzo et al., 1973; Tanaka et al., 1981; Jordan et al., 1970; Pape and Zabik, 1970). Pape and Zabik (1970) reported that the photolysis of ametryn under laboratory conditions did not occur at wavelengths greater than 300 nm, although photodegradation did occur in water at 253.7 nm. This result indicates that photolysis of ametryn in the environment is not appreciable. Rejto et al. (1983) have noted that the direct photolysis of s-triazine herbicides (including ametryn) exposed to visible light is so low that it is not likely to have environmental importance. However, Rejto et al. (1983), Tanaka et al. (1981) and Burkhard and Guth (1976) have shown that photosensitizers (riboflavin, surfactants and acetone) can significantly increase photodegradation of ametryn in the laboratory. Photosensitization may occur when molecules of a substance that absorbs light collide with the weak or non-absorbing molecule; energy is then transferred to a receiving molecule that becomes photolyzed (Jordan et al., 1970). Surface waters contain dissolved organic materials, such as humic substances, that strongly absorb UV and visible light, and can therefore act as photosensitizers for otherwise non-absorbing compounds (Burkhard and Guth, 1976). Humic acids found in soil have been found to interact with ametryn (Mueller-Wegener, 1977; Senesi, 1981; Senesi and Testini, 1982, 1983). Therefore, it may be possible for ametryn, in the aquatic environment, to undergo an undetermined rate of photolysis. The primary products of ametryn photolysis in the laboratory are the de-N-alkyl and the de-NN'-dialkyl s-triazines and the corresponding hydroxytriazines (Rejto et al., 1983; Burkhard and Guth, 1976).

Hydrolysis data specific to ametryn were not found in the available literature. Jordan et al. (1970) have noted that the s-triazine herbicides can be hydrolyzed to hydroxyanalogs, notably atrazine, simazine and propazine; however, ametryn does not contain a chlorine function as do the noted herbicides.

Volatilization data specific to ametryn in water were not found in the available literature. As noted in Section 2.3., Kearney et al. (1964) measured ametryn volatility from soils in the laboratory and found that ametryn was more volatile from wet soil than from dry soil.

In consideration of intermedia transport, Green et al. (1977) monitored sediments and runoff waters associated with two estuaries in Oahu, HI, to determine if herbicides (including ametryn) used in plantation crops reached coastal waters. It was concluded that ametryn underwent degradation in the soil and runoff waters at a sufficient rate to preclude its transport to coastal waters at levels that could be normally measured.

Kenaga (1980) has predicted the BCF values of ametryn, based on water solubility and K_{oc} , to be 33 and 21, respectively. Compounds having a BCF of over 1000 are those that, from experience, are most likely to need further evaluation for hazard assessment. The BCF values predicted for ametryn are <1000, and, therefore, indicate that it is not likely to be strongly bioconcentrated.

2.2. AIR

Specific data regarding the fate or transport of ametryn in the atmosphere were not located in the available literature.

Chemicals in the vapor phase may be adsorbed on aerosol particulates and removed from the atmosphere with the aerosol. It has been suggested by Cupitt (1980) that adsorption will be a reasonable vapor-phase removal

mechanism only for chemicals with saturation vapor pressures of $\leq 10^{-7}$ mm Hg. The vapor pressures of ametryn at 10°C and 20°C, respectively, are 1.9×10^{-7} and 8.4×10^{-7} mm Hg (WSSA, 1979), indicating that this compound may be expected to remain sorbed to particulate matter in the air. This particulate matter can be removed from the air via dry deposition to land or water, or via wet deposition (rain).

Photodegradation data (see Section 2.1.) indicates that ametryn in water did not photolyze at wavelengths >300 nm in the laboratory; therefore, ametryn in the air is not likely to undergo appreciable photolysis. It was also shown that ametryn could be photolyzed with sensitizers; whether particulate matter (to which ametryn may be sorbed) could act as such a sensitizer is not certain.

2.3. SOIL

The fate and transport of ametryn in soil have been studied more adequately than its fate and transport in the atmosphere and aquatic media. Microbial action probably accounts for the major breakdown of ametryn in the soil (WSSA, 1979).

Photodecomposition of ametryn in soil has not been evaluated under field conditions, but is expected to compare with prometryn, for which photodecomposition plays an insignificant role in soil loss (WSSA, 1979). The photolysis data (see Section 2.1.) indicates that some photodegradation may occur at the soil surface, but the rate is probably not important.

Although chemical hydrolysis is probably the principal pathway of initial degradation of the chloro-s-triazines (atrazine, simazine, etc.) in soil, it is doubtful that the methylthio-s-triazines (ametryn, etc.) are degraded initially through the same pathway to any significant extent,

except in very acidic soils (Goswami and Green, 1975); the results reported by Zimdahl et al. (1970) concerning degradation of ametryn in soil support this hypothesis. Goswami (1972) and Goswami and Green (1975) have studied the degradation of ametryn in Hawaiian soils. A laboratory comparison was made of autoclaved (sterile) versus inoculated (non-sterile) surface soils. Less than 7% of the applied ametryn was degraded in autoclaved soils, while ametryn was rapidly degraded in inoculated soils. The degradation in inoculated soils demonstrated the microbial involvement in soil degradation of ametryn. However, the degradation in sterile soil demonstrated that a measurable fraction of ametryn was degraded by a chemical mechanism. The degradation products from the autoclaved soils were primarily polar products, such as dealkylated ametryn and hydroxyatrazine. Obien (1970) has reported that the rate of hydrolysis of ametryn is less than half of that of atrazine in Hawaiian soils.

The biodegradability of ametryn in soils has been studied by several investigators. Fournier and Catroux (1980) showed that a number of isolated microorganisms, including Aspergillus fumigatus, Fusarium roseum graminearum, Mucor racemosus, Penicillium janthinellum and Pseudomonas crucivae, biodegraded ametryn. Soil microorganisms also effective in degrading ametryn were Arthrobacter sp., Microbacterium sp., Pseudomonas sp. (Bryant, 1963), A. fumigatus Fres (Kaufman, 1969) and Torulopsis sp. (Duke, 1964). Additionally, an organism tentatively identified as Rhizobium has been shown to biodegrade ametryn (Giardina and Buffone, 1977). As noted earlier, Goswami (1972) and Goswami and Green (1975) have presented evidence of microbial degradation of ametryn in Hawaiian soils. With respect to the Hawaiian soils studied, Goswami and Green (1972) have concluded: (1) detoxification and degradation of ametryn are relatively rapid in the surface horizon of

two important Hawaiian soils; (2) initially, ametryn is degraded in soil mainly through microbial N-dealkylation with simultaneous formation of some hydroxyatrazine; (3) complete metabolism of the ametryn ring by soil microorganisms is relatively slow and appears to be non-preferential or incidental; and (4) microbial degradation of ametryn involves not only polar-product formation and CO₂ evolution, but also assimilation of ametryn and/or its degradation products. Goswami (1972) has shown that an increase of organic matter in soil, such as sugarcane roots, accelerates ametryn degradation. The effects of temperature, pH and moisture content upon microbial degradation have not been adequately investigated.

The loss of ametryn through volatility from soil has not been investigated under field conditions. Kearney et al. (1964) measured ametryn volatilization from nickel-plated planchets at 25°C and found the rate to be equivalent to that of atrazine and prometryn. The volatility increased at 35°C and ametryn was less volatile from dry soil than from wet soil. By comparing the volatility of ametryn from soil with that of prometryn it can be predicted that soil losses via volatilization are insignificant (WSSA, 1979).

The transport of ametryn from soil by leaching has been studied. The leachability of ametryn from soil is related to its soil adsorption capacity. WSSA (1979) has made the following summary of ametryn adsorption and leaching characteristics in basic soil types:

"Ametryn is more readily absorbed on muck or clay soils than in soils of low clay or organic matter, and is seldom found below the upper few inches. The downward movement of leaching is limited by its adsorption to certain soil constituents and its comparatively rapid dissipation. The adsorption of ametryn in soils is greater than with most other commercial triazine herbicides, although this adsorption is readily reversible under most conditions. It has little lateral movement in soil except from erosion with soil particles."

Rodgers (1968) established the order of the leachability of the s-triazines as atratone>propazine>atrazine>simazine>ipazine>ametryn> prometryn in greenhouse and field experiments with Lakeland fine sand. Green and Young (1971) found that ametryn sorbed readily to most Hawaiian soils, especially those high in organic matter. Using the agitated slurry technique, Liu et al. (1970) found that adsorption of ametryn varied greatly among 34 Puerto Rican soils; adsorption was directly correlated with organic matter and silt content, but inversely correlated with pH of the soil. Liu et al. (1970) also found very little effect of temperature (from 5-45°C) on ametryn adsorption in Puerto Rican clay soils. Liu and Cibes-Vlade (1970) studied the leaching of ametryn in soil columns with differing rates of application and simulated rainfall. It was determined that the movement of ametryn in the soil was not a function of either rate of application or amount of water. Hance (1969) and Chang (1980) have both shown that ametryn adsorption decreases with an increase in soil pH. Virtually 100% adsorption of ametryn onto montmorillonite occurred at pH 5, but adsorption dropped to 20-40% at pH 8 (Hance, 1969). Mukhtar (1976) has studied the hysteresis (irreversibility) in the adsorption-desorption process for ametryn in various types of Hawaiian soils. The following was indicated: (1) desorption was generally slower than adsorption, and became still slower as the equilibrium time approached; (2) hysteresis increased with the magnitude of adsorption; and (3) hysteresis was larger where ionic attraction was the adsorption mechanism (usually at low pH). Helling and Dragun (1981) measured the comparative mobility of 25 herbicides in Hagerstown silty clay loam and in Mohlin clay loam by means of soil TLC and soil column leaching experiments. Ametryn had a low mobility (R_f of 0.23) in Mohlin clay loam and an intermediate mobility (R_f of 0.39) in Hagerstown loam.

Results from studies conducted in the continental United States indicated that the persistence of ametryn in soils (as a result of all microbial, chemical and physical processes) compares quite closely with that of prometryn (WSSA, 1979). Under normal conditions, prometryn persisted from 1-3 months (WSSA, 1979). Under the more tropical conditions of Hawaii and Puerto Rico, the residual life of ametryn in the soil often extended to several months, and ametryn may persist as long as atrazine (WSSA, 1979).

3. EXPOSURE

3.1. WATER

The mean concentration of ametryn in 999 samples of surface waters was reported in STORET to be 0.06816 $\mu\text{g/l}$ (range 0-12 $\mu\text{g/l}$). Printouts of the reporting stations indicate that this mean reflects detection of the high levels of ametryn in stream water in several locations, and does not imply widespread occurrence of detectable ametryn in ambient water; it appears that the ametryn was not detectable in most of the samples.

Green et al. (1977) monitored sediments and runoff waters associated with two estuaries in Oahu, HI, to determine if herbicides (including ametryn) used in plantation crops reached coastal waters. It was concluded that ametryn underwent degradation in the soil at a sufficient rate to preclude its transport to coastal waters at levels that could be normally measured.

Abstracts from foreign journals (Czechoslovakian and Hungarian) indicate that ametryn has been detected in trace amounts in selected ground and surface waters (Voznakova et al., 1982; Pal'usova et al., 1972; Kovac-Huber, 1982).

No data regarding ametryn in drinking water were found in the available literature.

3.2. FOOD

Ametryn is absorbed through both foliage and roots and appears to penetrate foliage rapidly, minimizing removal from foliage by rain. It translocates acropetally through xylem from roots and foliage, accumulating in the apical meristems, and is usually metabolized by tolerant plants (WSSA, 1979).

No mention was noted in the available literature of ametryn as an identified residue in American food. An abstract of a Danish article indicated that ametryn residue was detected in Danish food (Anderson, 1981).

3.3. INHALATION

Monitoring data for ametryn exposure in the air were not found in the available literature.

3.4. DERMAL

Monitoring data for ametryn exposure on the skin were not found in the available literature.

4. PHARMACOKINETICS

4.1. ABSORPTION

Qualitative evidence of absorption by rats of orally administered ametryn can be derived from the retention, distribution and excretion study by Oliver et al. (1969) (Sections 4.2., 4.3. and 4.4.). Following a single oral administration of [^{14}C]-isopropyl chain, [^{14}C]-ethyl chain or [^{14}C]-ring-labeled ametryn at a level of 1-4 mg/animal, Oliver et al. (1969) detected radioactivity in the urine, expired air and body tissues of dosed rats, indicating absorption of the administered radioactivity. Details regarding the kinetics of absorption of orally administered ametryn were not reported.

4.2. DISTRIBUTION

Oliver et al. (1969) studied the distribution of [^{14}C]-ring labeled ametryn to tissues of male and female rats given a single oral dose of the compound at a level of 1-4 mg/animal. The average percents of administered radioactivity in various tissues of treated animals are given in Table 4-1. At 6, 48 and 72 hours after dosing, the highest levels of radioactivity were seen in the blood, liver, lungs, spleen and kidneys of both sexes, whereas the lowest levels were seen in the heart, fat, muscle, brain and carcass. The authors considered the consistently higher level of activity in all tissues of treated female animals as compared to treated male animals to be due to hormonal differences between the sexes. Levels of radioactivity in all tissues except blood decreased over the 72 hours; levels of radioactivity in blood were 0.16, 0.15 and 0.19% recovery/g blood at 6, 48 and 72 hours, respectively, after dosing. Oliver et al. (1969) proposed that the blood levels would have decreased if observed over a longer time period. It

TABLE 4-1
Average Percent of Radioactivity in Tissues of Rats Given
Oral Doses of [¹⁴C]-Ring Labeled Ametryn^a

Organ	% Recovery/Gram		
	6 hours	48 hours	72 hours
Blood	0.16 ^b	0.15	0.19
Brain	0.04 ^b	0.01	0.01
Carcass	0.06	0.01	0.01
Fat	0.07	0.01	0.01
Heart	0.07 ^b	0.04	0.02
Kidneys	0.34 ^b	0.05	0.04 ^b
Liver	0.29	0.11 ^b	0.07 ^b
Lungs	0.11 ^b	0.06	0.05
Muscle	0.04	0.01	0.01
Spleen	0.31	0.06 ^b	0.05
Stomach	2.38	0.03	0.01

^aSource: Oliver et al., 1969

^bThe concentration of radioactivity in these tissues was significantly greater in females than in males, possibly due to hormonal differences (Oliver et al., 1969).

is noteworthy, however, that Hamboeck et al. (1981) found that the sulfoxide metabolite of ametryn, but not ametryn, covalently binds to the hemoglobin of rats in vitro to an extent >70% of the administered radioactivity.

4.3. METABOLISM

Oliver et al. (1969) examined the metabolism of [^{14}C]-isopropyl chain labeled ametryn, [^{14}C]-ethyl chain labeled ametryn, and [^{14}C]-ring labeled ametryn to $^{14}\text{CO}_2$ in both sexes of rats given an oral dose of one of the three radiolabeled compounds at a level of 1-4 mg/animal. Within 48 hours after dosing, mean percent recoveries of 41.9, 18.1 and 0.03% of the administered isopropyl, ethyl and ring labeled compounds, respectively, were obtained as $^{14}\text{CO}_2$ in the expired air of treated rats. The small amount of $^{14}\text{CO}_2$ excreted in respired air following administration of [^{14}C] ring ametryn may have been due to radioimpurities. Collection efficiency for $^{14}\text{CO}_2$ was reported to be 100%. Metabolism to $^{14}\text{CO}_2$ was rapid, as within 12 hours after dosing, 80 and 75% of the total expired $^{14}\text{CO}_2$ from ethyl and isopropyl labeled compounds, respectively, were excreted. These results indicate rapid metabolism (via dealkylation) of the alkylamino side chains (both isopropyl and ethyl) from the s-triazine ring to $^{14}\text{CO}_2$. Oliver et al. (1969) neither identified ametryn metabolites other than CO_2 nor proposed a plausible metabolic pathway for [^{14}C]-ring labeled ametryn.

4.4. EXCRETION

Oliver et al. (1969) examined the excretion of [^{14}C]-isopropyl chain labeled ametryn and [^{14}C]-ethyl chain labeled ametryn as $^{14}\text{CO}_2$ by rats, each given a single gavage dose of one of the compounds at a level of 1-4 mg/animal (Tables 4-2 and 4-3). Within 48 hours after dosing, the average percent recoveries of $^{14}\text{CO}_2$ for both sexes were 41.9 and 18.1%

TABLE 4-2

Average Percent Recovery of Radioactivity as $^{14}\text{CO}_2$ in Respired Air
of Rats Given Oral Doses of [^{14}C]-Isopropyl Labeled Ametryn^a

Hours After Dose	Average % Recovery			Cumulative % Recovery Over Time
	6 Males	6 Females	12 Rats ^b	
0-1	0.06	0.47	0.27	0.27
1-2	0.44	1.04	0.74	1.01
2-3	1.98	3.45	2.72	3.73
3-4	3.28	4.48	3.88	7.61
4-5	4.48	4.51	4.50	12.11
5-6	5.43	4.18	4.81	16.92
6-7	4.82	3.65	4.24	21.16
7-8	3.24	3.92	3.58	24.74
8-9	2.52	3.00	2.76	27.50
9-10	1.92	2.80	2.36	29.86
10-11	1.74	2.34	2.04	31.90
11-12	1.24	1.65	1.45	33.35
12-24	4.57	6.53	5.55	38.90
24-36	1.99	1.91	1.95	40.85
36-48	1.01	1.08	1.05	41.90
Total (0-48)	38.72	45.01	41.9	41.9

^aSource: Oliver et al., 1969

^bThe values in this column represent the average % recovery for both sexes, calculated from the two preceding columns of data.

TABLE 4-3

Average Percent Recovery of Radioactivity as $^{14}\text{CO}_2$ in Respired Air
of Rats Given Oral Doses of [^{14}C]-Ethyl Chain Labeled Ametryn^a

Hours After Dose	Average % Recovery			Cumulative % Recovery Over Time
	6 Males	6 Females	12 Rats ^b	
0-1	0.11	0.25	0.18	0.18
1-2	0.66	1.04	0.85	1.03
2-3	1.24	1.86	1.55	2.58
3-4	1.27	1.97	1.62	4.20
4-5	1.38	2.13	1.76	5.96
5-6	1.40	1.86	1.63	7.59
6-7	1.27	1.45	1.36	8.95
7-8	1.30	1.26	1.28	10.23
8-9	1.21	1.19	1.20	11.43
9-10	0.97	0.79	0.88	12.31
10-11	0.87	0.69	0.78	13.09
11-12	0.69	0.60	0.65	13.74
12-24	3.43	2.83	3.13	16.87
24-36	0.74	0.70	0.72	17.59
36-48	0.49	0.50	0.50	18.09
Total (0-48)	17.03	19.12	18.1	18.1

^aSource: Oliver et al., 1969

^bThe values in this column represent the average % recovery for both sexes, calculated from the two preceding columns of data.

of the administered dose of the isopropyl and ethyl labeled compounds, respectively. Excretion of both compounds as $^{14}\text{CO}_2$ was rapid, as 80 and 75% of the total respiratory excretion for the isopropyl and ethyl labeled ametryn, respectively, were complete within 12 hours after administration. There was no statistically significant difference between males and females in regard to the extent of respiratory excretion of $^{14}\text{CO}_2$.

When [^{14}C]-ring labeled ametryn was administered to rats under the same dose regime as discussed above, only 0.03% (mean for both sexes) of the administered dose was recovered as expired $^{14}\text{CO}_2$ in 48 hours (Oliver et al., 1969). This expired $^{14}\text{CO}_2$ may have been a result of radio impurities in the [^{14}C]-ring labeled compound. At 72 hours after administration of ring labeled compound, the average percent recoveries of radioactivity (parent compound and/or metabolites) in the urine and feces of both sexes were ~58 and 32%, respectively. Excretion via these two routes was rapid, as 75 and 50% of the total urinary and fecal recoveries, respectively, were detected within 24 hours after dosing (Tables 4-4 and 4-5). There was no statistically significant difference between males and females in regard to the extent of respiratory, urinary or fecal excretion of [^{14}C]-ring labeled ametryn and/or its metabolites.

TABLE 4-4

Average Percent Recovery of Radioactivity in the Urine of Rats Given
Oral Doses of [^{14}C]-Ring Labeled Ametryn^a

Hours After Dose	Average % Recovery			Cumulative % Recovery Over Time
	Males	Females	Both Sexes ^b	
0-6	18.75	16.81	17.78	17.78
6-12	21.28	23.90	22.59	40.37
12-24	12.06	11.58	11.82	52.19
24-36	3.07	3.10	3.40	55.59
36-48	1.03	1.17	1.10	56.69
48-60	0.46	0.65	0.56	57.25
60-72	0.27	0.40	0.34	57.59
Total (0-72)	57.55	57.61	57.6	57.6

^aSource: Oliver et al., 1969

^bThe values in this column represent the average % recovery for both sexes, calculated from the two preceding columns of data.

TABLE 4-5

Average Percent Recovery of Radioactivity in the Feces of Rats Given
Oral Doses of [^{14}C]-Ring Labeled Ametryn^a

Hours After Dose	Average % Recovery			Cumulative % Recovery Over Time
	Males	Females	Both Sexes ^b	
0-6	0.18	0.07	0.13	0.13
6-12	3.25	0.09	1.67	1.80
12-24	17.91	13.92	15.92	17.73
24-36	7.43	10.36	8.90	26.62
36-48	2.58	4.45	3.52	30.14
48-60	2.13	1.07	1.60	31.74
60-72	0.36	0.37	0.37	32.11
Total (0-72)	33.84	30.33	32.1	32.1

^aSource: Oliver et al., 1969

^bThe values in this column represent the average % recovery for both sexes, calculated from the two preceding columns of data.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of ametryn were not located in the available literature. Ametryn has not been scheduled for testing in a carcinogenesis bioassay by the National Toxicology Program (NTP, 1983).

5.2. MUTAGENICITY

Ametryn was negative in several genotoxicity assays, including the reverse mutation assay with Salmonella typhimurium in the absence of a mammalian metabolic activation system (Andersen et al., 1972), the Rec-assay with Bacillus subtilis, strains H17 Rec⁺ and M45 Rec⁻ (Shirasu, 1975; Shirasu et al., 1976), the mitotic gene conversion assay with a diploid strains of Saccharomyces cerevisiae (Siebert and Lemperle, 1974), and the aneuploid production assay with Neurospora crassa (Griffiths, 1979). These genotoxicity tests are summarized in Table 5-1.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of ametryn were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the other reproductive effects of ametryn were not located in the available literature.

5.5. CHRONIC TOXICITY

Pertinent data regarding the chronic or subchronic toxicity of ametryn were not located in the available literature.

5.6. OTHER RELEVANT INFORMATION

The oral LD₅₀s for ametryn in rats and mice have been reported to be 1750 and 965 mg/kg, respectively (NIOSH, 1983). The dermal LD₅₀ for ametryn in rabbits has been reported to be 8160 mg/kg (NIOSH, 1983).

TABLE 5-1
Genotoxicity Testing of Ametryn

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Reference
Reverse mutation	<u>Salmonella typhimurium</u>	spot test	-1-5 µg/plate	None	-	Andersen et al., 1972
Rec-assay	<u>Bacillus subtilis</u> H17 Rec ⁺ M45 Rec-	spot test	NR	None	-	Shirasu 1975; Shirasu et al., 1976
Mitotic gene conversion	<u>Saccharomyces cerevisiae</u> diploid strain	cell culture	1000 ppm	None	-	Siebert and Lempert, 1974
Aneuploid production	<u>Neurospora crassa</u>	NA*	NR	None	-	Griffiths, 1979

*Cells were exposed in solid media, and after fertilization, the ascospores were harvested and plated on selective media at a level of -10^6 .

NA - Not applicable

NR - Not reported

A dose of 76 mg of ametryn caused irritation to the eyes of rabbits (NIOSH, 1983). Ametryn has been reported to cause skin sensitization in guinea pigs and contract allergic dermatitis in humans (Bainova, 1979).

A single oral dose of ametryn at a level of 879 mg/kg to mice at 5 days before, the same day as, or 2 days subsequent to immunization with sheep erythro-cytes resulted in statistically significant ($p < 0.05$) decreased numbers of splenic plaque-forming cells in treated animals (Wilttrout et al., 1978; Ceglowski et al., 1979). A similar depression in the number of antibody plaque-forming cells, however, was not seen in mice dosed orally with ametryn at a level of 88 mg/kg as a single dose or as daily doses for 8 or 28 days before immunization with sheep erythrocytes.

6. AQUATIC TOXICITY

6.1. ACUTE EFFECTS

The acute lethality of ametryn has been determined in two freshwater and two marine species (Table 6-1). The euryhaline striped mullet, Mugil cephalus, appears most sensitive to ametryn, having a 96-hour LC_{50} of 0.68 mg/l (Tag El-Din et al., 1981). The estuarine spot, Leiostomus xanthurus, had no toxic effects or mortality when exposed at 1.0 mg/l for up to 48 hours (Butler, 1965).

Acute toxicity testing with the freshwater rainbow trout, Salmo gairdneri, has resulted in 96-hour LC_{50} values of 8.8 (Schneider, 1979) and 3.2 mg/l (Johnson and Finley, 1980). Schneider (1979) also reported 24- and 48-hour LC_{50} values of 17.0 and 11.8 mg/l, respectively, indicative of a dose-related response. The 96-hour LC_{50} reported by Johnson and Finley (1980) for the bluegill sunfish, Lepomis macrochirus, was 3.7 mg/l; the bluegill was only slightly more resistant than the trout in studies by the same researchers.

Butler (1965) reported results of acute toxicity testing of ametryn in the brown shrimp, Penaeus aztecus, and oyster, Crassostrea virginica. Shrimp were exposed at 1.0 mg/l with no visible effects after 24 hours of exposure but 10% mortality within 48 hours of exposure. Shell growth was measured as an indicator of toxic effects in the oysters. After 96 hours of exposure at 1 mg/ametryn/l, shell growth was retarded ~14% in exposed oysters and required ~1 week for recovery.

6.2. CHRONIC EFFECTS

Pertinent data on the chronic toxicity of ametryn on aquatic organisms were not located in the available literature.

TABLE 6-1
Acute Lethal Effects of Ametryn to Fish

Species	Duration	Concentration (mg/L)	Method	Effect	Reference
Rainbow trout, <u>Salmo gairdneri</u>	96	3.2	static	LC50	Johnson and Finley, 1980
Rainbow trout, <u>S. gairdneri</u>	48	3.4	static	LC50	FWPCA, 1968
Rainbow trout, <u>S. gairdneri</u>	24	17.0	static	LC50	Schneider, 1979
Rainbow trout, <u>S. gairdneri</u>	48	11.8	static	LC50	Schneider, 1979
Rainbow trout, <u>S. gairdneri</u>	96	8.8	static	LC50	Schneider, 1979
Bluegill sunfish, <u>Lepomis macrochirus</u>	96	3.7	static	LC50	Johnson and Finley, 1980
Mullet, <u>Mugil cephalus</u>	96	0.68	NR	LC50	Tag El-Din et al., 1981
Spot, <u>Leiostomus xanthurus</u>	48	1.0	flow-through	no effect	Butler, 1965

NR = Not reported

6.3. PLANT EFFECTS

Ametryn is used as a herbicide in the control of floating aquatic plants such as water hyacinth and alligator weed (Weldon and Blackburn, 1967). It is effective when applied at ~3 lb/A, and appears to be persistent. Ahmed et al. (1980) reported that ametryn at 112 mg/m² partially killed water hyacinth. Ametryn was also reportedly very effective in killing or controlling duckweed when applied at 0.00195-1.00 mg/l in the water (Liu and Maldonado, 1979).

The toxic effects of ametryn on algae have been reported by several researchers. Walsh (1972) reported that ametryn at 0.010 mg/l caused a 50% decrease in growth in the marine algae Chlorococcum sp. and Isochrysis galbana, and caused oxygen production to decrease by 50% in I. galbana and Phaeodactylum tricornutum. At 0.020 mg/l, growth was decreased (50%) in P. tricornutum, and oxygen production was decreased in Chlorococcum sp. Dunaliella tertiolecta was more resistant, having oxygen evolution and growth reduced by 50% after exposure to 0.040 mg ametryn/l. In an English abstract of a German study (Tscheu-Schlueter, 1976), ametryn was noted as a very potent inhibitor of photosynthesis in the alga Ankistrodesmus falcatus.

6.4. RESIDUES

Pertinent data on the persistence of ametryn or its residues in aquatic organisms were not located in the available literature.

6.5. OTHER RELEVANT INFORMATION

Additional data pertinent to the toxic effects of ametryn on aquatic organisms were not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Tolerances have been set by the U.S. EPA at 0.1 ppm for ametryn residues in or on cassava roots (Federal Register, 1983b) and at 0.25 ppm for ametryn residues in or on taro and yams (Federal Register, 1983a) and bananas, pineapples, pineapple fodder and forage, potatoes, sugarcane, and sugarcane fodder and forage (Federal Register, 1969).

7.2. Aquatic

Guidelines and standards for the protection of aquatic organisms from the toxic effects of ametryn were not located in the available literature.

8. RISK ASSESSMENT

Carcinogenicity and subchronic and chronic toxicity studies of ametryn were not located in the available published literature. Negative results were obtained for ametryn in genotoxicity assays with Salmonella typhimurium (Andersen et al., 1972), Bacillus subtilis (Shirasu, 1975; Shirasu et al., 1976), Saccharomyces cerevisiae (Siebert and Lemperle, 1974), and Neurospora crassa (Griffiths, 1979). Ametryn causes eye irritation in rabbits (NIOSH, 1983), skin sensitization in guinea pigs (Bainova, 1979) and contact allergic dermatitis in humans (Bainova, 1979). At a level close to the LD₅₀, oral administration of a single dose of ametryn resulted in depressed splenic plaque-forming cells in treated mice (Wiltrout et al., 1978; Cegłowski et al., 1979).

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews animal data that can be used in risk assessment. Based on a NOAEL of 10 mg/kg bw/day for liver effects in rats in a subchronic feeding study, and using an uncertainty factor of 1000 (10 to account for interspecies extrapolation, 10 for protection of unusually sensitive individuals within the population and 10 for the use of a subchronic study for ADI derivation), an ADI of 0.01 mg/kg bw/day or 0.7 mg/day for a 70 kg man was derived.

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APPENDIX:
LITERATURE SEARCHED

This data summary is based on computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Base
SANSS
AQUIRE

These searches were conducted in November, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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